Remarks

Rejection of Claims 25-26 under 35 U.S.C. §112 first Paragraph

Claims 25 & 26 have been rejected under 35 U.S.C. §112 first paragraph because it is asserted that while being enabled for treating nausea and/or vomiting and/or motion sickness in a mammal, the specification does not enable the prevention of these ailments. Applicants respectfully traverse these rejection and request that they be withdrawn.

Attached are 2 exhibits, which clearly show that it was well known in the art at the priority date of the present invention that scopolamine could prevent nausea, vomiting and motion sickness. Please note Exhibit A, which contains page 890 and the Title page of the Physician's Desk Reference of 1997, prior to the date of the filing of the present application. This Exhibit shows that scopolamine not only is effective but was approved by the United States' Food and Drug Administration for the prevention of nausea and vomiting associated with motion sickness. One of ordinary skill in the art at the time of the priority date would be able to safely predict that the intranasal administration of scopolamine would be effective in preventing nausea and vomiting and motion sickness based upon the fact that the transdermal administration of scopolamine was effective.

Exhibit B contains pages 158, 592 and the Title page of Goodman & Gilman's *The Pharmacological Basis of Therapeutic* 9th Ed (1996). On pages 158 and 592 it is clearly disclosed that scopolamine can be used to prevent nausea associated with motion sickness.

International PCT Application No. WO 83/00286 (The Keith Application) also shows that intranasal scopolamine can be used to prevent vomiting and nausea associated with motion sickness. See Examples IV - XII on pages 4-6 of the Keith application.

Applicants contend that that one of ordinary skill in the art would easily predict that the intranasal scopolamine formulation of the present invention would be able to both prevent and treat motion sickness and the associated nausea and vomiting based upon the fact that the U.S. Food and Drug Administration has approved scopolamine for such a use (Exhibit A), the Authors in Goodman and Gilman's *The Pharmacological Basis of Therapeutic* 9th Ed (1996) teach that scopolamine can be so used, and the Keith application clearly shows data indicating that intranasal scopolamine is also effective to prevent and treat nausea associated with motion sickness. Thus, all of the factors of *In re Wands* have been clearly met.

Base upon the reasons discussed above, Applicants respectfully assert that the rejection of claims 25 & 26 have been overcome, and respectfully request that the rejection be withdrawn and the claims as amended be allowed.

Rejection of Claims 23 -26 under 35 U.S.C. §112 Second Paragraph

Claims 23 – 26 have been amended as the Examiner has suggested. Applicants respectfully request that the rejection under 35 U.S.C. §112 second paragraph be withdrawn.

Rejection of Claims 23 – 26 under 35 U.S.C. §103(a)

The claims have been rejected under 35 U.S.C. §103(a) as being unpatentable over Keith (WO 83/00286) in view of Joshi *et al.* (U.S. Patent No. 5,252,818) and *Handbook of Pharmaceutical Excipients,* 2nd Ed. Page 383. Applicants respectfully traverse the rejection and request that it be withdrawn for the reasons listed below.

A *Prima facie* Case of Obviousness Has Not Been Established

A *prima facie* case of non-obviousness has not been established. The rejection of the claims is not based upon an examination of the invention as a whole with the unexpectedly superior properties of the claimed intranasal formulation as is required by law. The rejection is based upon the examination of the elements and a hindsight reconstruction of the claims using the applicants' specification. This is an impermissible rejection under U.S. Law. One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention. Furthermore, obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching or suggestion supporting the combination. See, *In re Fine,* U.S.P.Q 2d 1596 (Fed. Cir. 1988). Nothing in the prior art suggests the claimed formulation for intranasal scopolamine.

The cited references do not disclose or suggest the claimed invention as a whole. The primary reference PCT Application Publication no. WO 83/00286 (hereinafter referred to as the Keith reference) discloses an aqueous intranasal formulation with up to 20% ethanol. It actually teaches away from the claimed invention in that such a formulation would have a relatively high

pH of about 7 because is contains only water and ethanol, the ethanol having no effect on pH. This is in contrast to the claimed formulation which dictates that the pH must be at about 3.5. Furthermore the Keith reference teaches away from the claimed invention because the '286 contains no buffering salt, while the claimed invention must have a buffer salt concentration of about 20 mM to maintain the pH of 3.5.

The secondary references, U.S. Patent No. 5,252,318 (hereinafter the Joshi patent), and the *Handbook of Pharmaceutical Excipients,* 2nd E, page 383 (hereinafter the 'Handbook') also do not add any additional teachings that would create a *prima facie* case of obviousness of the present invention.

The Joshi patent discloses the production of "reversibly gelling compositions", a composition that is initially a liquid but changes to a gel upon a change in temperature or pH. See column 3, line 2 - 24. The present invention is not a reversibly gelling composition. In fact the Joshi patent gives a list of gelling agents, which exhibit reversible gelation in response to variations in pH and temperature on column 6 lines 39 to column 7 line 25, and polyvinyl chloride is not listed as a gelling agent. Thus, Joshi teaches away from the present invention. Moreover, Joshi *et al.* teach that a preferred embodiment contains methyl cellulose, (column 7 lines 5 – 11). The claimed invention however, excludes the use of methyl cellulose in fact Example 5, page 33 of the present invention directly compares an intranasal scopolamine composition containing methyl cellulose and one that contains PVA, and the PVA formulation of the present invention was **unexpectedly more stable**. See page 33 lines 15 – 24 of the present specification, which state the following:

As is evident from a review of the results of Table 23, the nasal gel formulation prepared according to the present invention with polyvinyl alcohol as a gelling agent in a formulation about pH 3.5 and concentration of 20 mM (Formulation 2) maintains a substantially constant viscosity over time, thus evidencing that such formulations remain chemically and physically stable for periods of 6 months. The nasal gel formulation prepared with methyl cellulose as a gelling agent in a formulation at about pH 3.5 and concentration of 25 mM (Formulation 1) demonstrates a significant decrease in viscosity after only one month of storage, with a remarkable decrease 6 months after storage, thus evidencing that such a formulation is chemically and physically unstable.

The 'Handbook reference only states that PVA is a viscosity increasing/lubricating agent but gives no direction as far as proper pH or salt concentration or that it would be appropriate to add to a scopolamine formulation let alone an intranasal scopolamine formulation.

Other Unexpected Superior Properties.

New claims 23 –26 embody the formulation 2 of Example 1. Table one clearly shows that Formulation 2 embodied in claims 23 – 26 produced expectedly higher levels of scolpolamine being absorbed into the blood stream when administered intranasally as compared to a the prior art composition of Formula 1. See Example 2 pages 15 and 16.

Another unexpectedly superior property of Formulation 2, the claimed invention, is the rapid onset of the drug as is evidenced by the graph which shows scopolamine free base concentrations of Formulation 2 more than doubled that of Formulation 1 in five minutes. See Example 2 page 16. Please note that the data from Example 2 are results from the administration of the scolpolamine hydrobromide to HUMANS. These are human data.

APPLICANTS HAVE SUCCESSFULLY OVERCOME THE ALLEGED *PRIMA FACIE* CASE OF OBVIOUSNESS

Even if a proper *prima facie* case had been in established in the office action, which applicants maintain was not done, the applicants have overcome the alleged *prima facie* case by the evidence of nonobviousness, *i.e.*, the unexpected superior properties of the claimed intranasal scopolamine formulation of the present invention.

REQUEST FOR AN INTERVIEW

The undersigned attorney respectfully requests an interview prior to a Final Office action being submitted.

Based upon the amendment (especially the very narrowing amendment) and the discussion above, applicants assert that the rejection of the claims under 35 U.S.C. §103(a) has been overcome. Applicants request that the rejection be withdrawn and the claims allowed.

Should there remain unresolved issues, it is respectfully requested that the Examiner telephone Paul G. Lunn, Applicants' Attorney at (425) 908-3643 so that such issues may be resolved as expeditiously as possible.

Respectfully Submitted,

Paul D. Lunn

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Date

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Enclosures:
Exhibit A, page 890 and the Title page of the Physician's Desk Reference of 1997
Exhibit B, pages 158, 592 and the Title page of Goodman & Gilman's *The Pharmacological Basis of Therapeutic* 9th Ed (1996). (4 pages total)

I hereby certify that this correspondence, of 19 pages total is being transmitted by facsimile to the U.SPTO to the fax number ~~(703) 308-4556~~ 703 872-9306 on September 15, 2004:
Sent by facsimile by Leslie Kodish, signature Leslie M. Kodish on the above date.